REMARKS

Applicants confirm that the statement in the previous response regarding the claims in the case being claims 19-36 was made in error. The Examiner correctly points out that the claims currently under consideration are claims 1-31 and 71. Claims 32-70 have been withdrawn from consideration.

In this Amendment, claims 2-5, 8-11, 13, 19-25, and 28-70 are canceled. Claims 72 and 73 are added. Thus, upon entry of this amendment, the claims in the case will be claims 1, 6, 7, 12, 14-18, 26, 27, and 71-73.

Applicants note with appreciation the withdrawal of the written description rejection of claims 7 and 15, the anticipation rejection of claims 1, 4, and 13 over Aronshtam, the obviousness rejection of claims 1, 3, 18, and 23 over Wu in view of Winnacker, the obviousness rejection of claims 1, 6, 7, 14, 15, 17, 18, 20, 24-27, and 71 over Nicolaides in view of Winnacker and Aronshtam, and the obviousness-type double patenting rejection of claims1, 6, 7, 14, 15, 17, 18, 20, 24-27, and 71 over claims 1-10 of U.S. Patent 6,146,894 in view of Winnacker and Aronshtam as detailed in paragraph 4 of the Office Action.

The Specification

Applicants have amended the specification to remove embedded hyperlinks. In addition to the hyperlink identified by the Examiner on page 12 of the Specification, Applicants have found two additional hyperlinks and have amended the Specification to remove these as well. Each hyperlink has been replaced with a written description of the Uniform Resource Locator or web address that accesses each hyperlink. For example,

"www.ehs.utah.edu/ohh/mutagens" has been amended to "the website having the URL address: www host server, ehs.utah.edu domain name, ohh directory, mutagens subdirectory". Applicants respectfully submit that the Specification is in proper form.

Amendments to the claims

Please cancel claims 2-5, 8-11, 13, 19-25, and 28-70 without prejudice and without disclaimer as to the subject matter thereof. Claims have been canceled to limit the issues in this application. However, Applicants do not concede the correctness of the rejections applicable to any of these claims, and expressly reserve the right to pursue these claims in one or more divisional applications.

Please add claims 72 and 73. These claims find support, for example, in claims 11 and 22 as originally filed. The spelling of "PMS2L" has been corrected in the claims, consistent with that provided in the Specification at page 18, line 14. Thus, no new matter is added.

Claims 1 and 18 have been amended to include the feature that the polynucleotide encodes a form of a PMS2 mismatch repair protein. Support for the amendment may be found throughout the Specification and in claims 4 and 19 as originally filed.

Claim 18 has been amended to include the feature that the bacterial culture is induced. Support for the amendment may be found, for example, in the Specification at page 13, lines 16-30.

Claim 71 has been amended to provide appropriate antecedent basis.

Other amendments to claims have been made for clarification purposes.

Claim rejections

The Office Action maintained the rejection of claims 18, 19, and 25 under 35 U.S.C. §102(b) over Aronshtam *et al.* (1996) *Nucl. Acids Res.* 24:2498-2504 ("Aronshtam") and claims 1-6, 8-14, 16, 18-25 and 28-31 under the "Written Description" Requirement of 35 U.S.C. §112, first paragraph. Furthermore, new grounds of rejection were presented under 35 U.S.C. §112, second paragraph and 35 U.S.C. §102(b). Each will be addressed in turn.

(a) 35 U.S.C. §102(b) over Aronshtam

The Office Action maintained the rejection of claims 18, 19, and 25 under 35 U.S.C. §102(b) over Aronshtam *et al.* (1996) *Nucl. Acids Res.* 24:2498-2504 ("Aronshtam"). Claims 19 and 25 have been canceled, thus the rejection is moot with respect to these claims and the following remarks are directed to claim 18 only.

The Office Action indicates that the rejection of these claims is maintained as the claims do not include the feature of induction of bacteria. Claim 18 is herein amended to include the feature that the cultures of bacteria are induced. As Aronshtam does not teach induction of bacteria, the claims are not anticipated by Aronshtam. Withdrawal of the rejection under 35 U.S.C. §102(b) over Aronshtam is respectfully requested.

(b) 35 U.S.C. §112, first paragraph "Written Description"

The Office Action rejects claims 1-6, 8-14, 16, 18-25 and 28-31 under the "Written Description" Requirement of 35 U.S.C. §112, first paragraph.

The Office Action asserts that the claims are not adequately described because they encompass a genus of mismatch repair proteins of which a sufficient number of species have not been described.

As an initial matter it is noted that claims 2-5, 8-11, 13, 19-25, and 28-31 have been canceled. Thus, the following remarks address only remaining claims 1, 6, 12, 14, 16, and 18, and newly presented claims 72 and 73.

Claims 1 and 18 are the only pending independent claims of the rejected claim set. Claim 1 is directed to a method for making a hypermutable bacterium. A polynucleotide encoding a form of a PMS2 mismatch repair protein under the control of an inducible transcription regulatory sequence is introduced into a bacterium. The inducible transcription regulatory sequence is induced. The PMS2 mismatch repair protein exerts a dominant negative effect of mismatch repair when expressed in the bacterium. The bacterium becomes hypermutable.

Claim 18 is directed to a homogeneous composition of cultured, hypermutable bacteria which comprise a polynucleotide encoding a form of a mismatch repair protein under the control of an inducible transcription regulatory sequence. The mismatch repair protein is a PMS2 mismatch repair protein. The PMS2 mismatch repair protein exerts a dominant negative effect when expressed in bacteria. The bacteria are induced.

The statutory authority for the written description requirement is 35 U.S.C. §112, first paragraph, which states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it most nearly connected, to make and use the same,

> and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In a recent Federal Circuit decision, *Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc. v. Diamond Automation, Inc.* 2003 U.S. App. LEXIS 6285 (Fed. Cir. 2003), the Federal Circuit discussed the Written Description requirement at length (a copy of the case is attached for the Examiner's convenience). In *Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc. v. Diamond Automation, Inc.*, the Federal Circuit explained that its own case law shows two primary goals in the written description requirement. The first is embodied in its opinion in *In re Wertheim* 541 F.2d 257, 191 USPQ 90 (CCPA 1976), and the second is embodied in its opinion in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). In *In re Wertheim*, the court noted that "the function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter *later* claimed by him." 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In other words, as restated more recently by the Federal Circuit:

> The purpose of the written description requirement is to prevent an applicant from *later* claiming that he invented that which he did not; the applicant for a patent is therefore required "to recount his invention in such detail that his *future claims can be determined to be encompassed within his original creation.*"

Amgen Inc. v. Hoechst Merion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)(citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (emphasis added).

The second goal of the written description requirement, as first set forth in *Regents of the University of California v. Eli Lilly & Co.*, applied the written description requirement to adequacy of a description in a case involving a DNA sequence. The Federal Circuit held that a precise definition of the DNA sequence was required to satisfy the written description requirement, even in the absence of priority issues. The Court has further refined this rule in such cases as *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1069 (Fed. Cir. 2002) and *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). In *Amgen*, the Federal Circuit clarified its holding in *Regents* (*Lilly*), stating: "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure." *Moba* at 30 (citing *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d at 1332).

The subject claims, as amended, do not go beyond the scope of the claims as originally filed, and thus satisfy the first goal of the written description requirement that the Applicants had possession of the claimed invention (*i.e.*, there is no issue of later claiming).

Further, the Applicants have satisfied the second goal of the written description requirement by showing that "the disclosed function is sufficiently correlated to a particular known structure." That is, the Applicants provided a demonstration that PMS2 proteins expressed in bacteria exert a dominant negative effect. Applicants demonstrated in Example 2 that dominant negative forms of PMS2 proteins, human PMS2-134 and *Arabidopsis thaliana* PMS2-134 dominantly negatively affect mismatch repair when

expressed in bacteria. Applicants also demonstrated in Example 2 that a human PMS2-related gene, PMSR3, dominantly negatively effects mismatch repair in bacteria. Thus, Applicants demonstrated that PMS2-related proteins and truncated homologous PMS2 proteins from humans and plants inhibit mismatch repair in bacteria. Applicants were in possession of the invention and have described the invention through representative examples of proteins which have a dominant negative effect on mismatch repair in bacteria.

Further, the fact that PMS2 proteins from disparate species, such as plants and humans, function in the same way indicates to one of skill in the art that PMS2 proteins in more closely related species, (such as mammals, for example,) would function in the same manner. This, in fact, is true. The mouse PMS2 gene was cloned and sequenced prior to the effective filing date of the application, February 11, 2000. The nucleic acid and amino acid sequence of the mouse PMS2 gene were published under GenBank Accession Number U282724.1 on February 9, 1996. (Exhibit A.) The amino acid sequence encoded by the mouse PMS2 gene shares 73% amino acid sequence identity and 80% amino acid sequence homology with the amino acid sequence encoded by the human PMS2 gene shown in SEQ ID NO:17. (Exhibit B.) Narayanan *et al.* (*Proc. Natl. Acad. Sci. USA* (1997) *94*:3122-3127; Exhibit C) teaches that "mice nullizygous in *Pms2* showed a 100-fold elevation in mutation frequency in all tissues examined compared with both wild-type and heterozygous littermates."[1] (Page 3122, lines 8-11.) Thus, the Applicants provide strong evidence that the broad scope of PMS2 homologs from a wide variety of species would be expected to perform in the same way.

[1] An elevated mutation frequency is an indication of decreased mismatch repair.

The Applicants also demonstrate, as noted by in the Office Action, that the human MutL homolog, PMSR3, when expressed in bacteria, produces a mutator phenotype. Nicolaides *et al.* identified seven PMSR genes (PMS2 related genes) (Nicolaides *et al.* (1995) *Genomics* 30:195-206). Nicolaides showed that PMSR2, PMSR3, PMSR6, and PMS2L proteins are highly homologous to the N-terminal portion of PMS2 (*i.e.*, the PMS2-134 deletion mutant) (See Nicolaides *et al.* Figure 5E and PubMed NM_005395 (cited in Specification at page 18, line 15)). Thus, one of skill in the art, having the knowledge of the structural similarity of PMSR3 to PMS2L and the other PMSR proteins and the knowledge of PMSR3's functional behavior in *E. coli*, would predict that the PMSR family of proteins and PMS2L would induce a hypermutable phenotype in bacteria. Thus, claims 72 and 73 are also adequately described.

Applicants have fulfilled the Federal Circuit's guidelines in *Lilly* as interpreted by the Federal Circuit in *Moba* that the written description "requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure." Thus, Applicants have provided an adequate written description to support the claimed invention. Withdrawal of the rejections under 35 U.S.C. 112, first paragraph is respectfully requested.

(c) 35 U.S.C. §112, second paragraph

The Office Action rejects claims 2-5, 12, 13, 16 and 71 under 35 U.S.C. §112, second paragraph. Applicants have canceled claims 2-5, and 13. Thus the newly presented ground of rejection under 35 U.S.C. §112, second paragraph as applied to claims 2-5 and 13 is moot.

Applicants have amended claims 12 and 16 to depend from claim 1, which has been amended to incorporate the feature that the mismatch repair gene is a PMS2 protein.

Applicants have amended claim 71 to recite a "polynucleotide encoding a form of a PMS2 mismatch repair protein" rather than a "dominant negative allele" to provide sufficient antecedent basis in the claim. Claim 71 has been further amended to depend from claim 1 rather than canceled claim 3.

It is respectfully submitted that the claims are sufficiently definite.

(d) 35 U.S.C. §102(b)

The Office Action rejects claims 1, 3, 18, 23 and 25 under 35 U.S.C. §102(b) over Prudhomme *et al.* (1991) *J. Bacteriol.* 173:7196-7203 ("Prudhomme") alleging that Prudhomme teaches expression of the *Streptococcus pneumoniae* gene *hexA* in *Escherichia coli* under the control of a hybrid promoter, macp, which requires both maltose and one of either lactose or IPTG to drive expression. The Office Action further states that *hexA* is a homolog of *E. coli MutS*, and that the induced bacteria were hypermutable.

Without conceding the correctness of the Examiner's argument, claims 3, 23 and 25 have been canceled rendering the argument against the patentability of these claims moot. Claims 1 and 18 have been amended to incorporate the feature that the mismatch repair protein is a PMS2 protein. Prudhomme neither teaches nor suggests the use of PMS2. Thus, Prudhomme does not anticipate the claims as amended.

The Office Action also rejects claims 1, 3, 10, 18, 23, 24, 28 and 31 under 35 U.S.C. §102(b) over Fishel *et al.* (1993) *Cell* 75:1027-1038 ("Fishel") alleging that Fishel

teaches expression of the human gene *MSH2* in *E. coli* under control of the lac promoter which requires IPTG for induction, and that *MSH2* is a homolog of *MutS*.

Without conceding the correctness of the Examiner's argument, claims 3, 10, 23, 24, 28 and 31 have been canceled rendering the argument against the patentability of these claims moot. Claims 1 and 18 have been amended to incorporate the feature that the mismatch repair protein is a PMS2 protein. Fishel neither teaches nor suggests the use of a PMS2 protein. Thus, Fishel does not anticipate the claims as amended.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b).

Conclusion

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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